REMARKS

Applicants have amended the title to more specifically describe the invention. The specification has been amended to capitalize trademarks and remove reference to embedded hyperlinks. Submitted herewith is a response to the Notice to Comply, which amends the specification to include a copy of the sequence listing.

Applicants have cancelled Claims 1-3, 7-10 and 15 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claims 4-6, 11-12, and 14 to remove reference to the Figures. Claims 4-5 have been amended to add the limitation that the claimed nucleic acids are more highly expressed in normal stomach compared to stomach tumor. Applicants have amended Claims 4, 5, 6 and 14 to delete elements (a)-(d). Claim 14 is amended to include "or a complement thereof" to amended elements (a)-(c), to specify the conditions under which hybridization occurs, and to add the following text "wherein said isolated nucleic acid molecule is suitable for use as a PCR primer, or probe; and wherein said isolated nucleic acid is at least about 20 nucleotides in length." Claim 16 is amended to read "at least about 50 nucleotides in length." Claim 17 is amended to depend from Claim 4. New Claims 21-31 have been added.

Applicants maintain that the amendments add no new matter and are fully supported by the specification as originally filed. Support for the amendments to Claims 4-5 can be found, for example, in Example 18 beginning at paragraph [0529], as well as paragraph [0336] of the specification. Support for the amendments to Claim 14 can be found, for example, at paragraphs [0012], [0227], [0317], and [0327] of the specification. Support for the amendment to Claim 16 and new Claims 21-25 can be found, for example, at paragraph [0012]. Support for new Claims 26-31 can be found, for example, in the claims as originally filed, and paragraphs [0227] and [0317].

Claims 4-6, 11-14, and 16-31 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed February 7, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Specification:

The PTO has objected to the title as not being descriptive. Applicants have amended the title herein.

The PTO has stated that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). The PTO states that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825 because the application does not contain, as a separate part of the disclosure on a paper copy, a "Sequence Listing" as required by 37 C.F.R. § 1.821(c).

Applicants submit herewith a response to the Notice to Comply which amends the specification to include a paper copy of the "Sequence Listing," which is also submitted herewith.

IDS:

The PTO has requested additional information on the references cited in the BLAST results reported in the Information Disclosure Statement filed September 17, 2002. Applicants submit herewith more detailed information regarding the cited sequences (attached as Exhibit 1).

Priority Determination:

The PTO has stated that because the claimed nucleic acid has no utility, the priority under 35 U.S.C. § 120 is set at the instant filing date, May 8, 2002. Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 5, 2002. The preliminary amendment states that the instant application "is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims

priority under 35 U.S.C. § 120 to US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 USC §371 of PCT Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 USC §119 to US Provisional Application 60/101475 filed 9/23/1998."

Applicants submit that for the reasons stated below, the claimed nucleic acids have a credible, substantial, and specific utility. The sequences of SEQ ID NOs: 113 and 114 were first disclosed in US Provisional Application 60/101475 filed 9/23/1998 in Figures 1 and 2A-B. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants are entitled to the benefit of these earlier-filed applications.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has rejected Claims 1-6, 8-10 and 14-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO objects to the phrase "the extracellular domain" as PRO1446 is not disclosed as being expressed on a cell surface. The PTO further objects to the recitation of "the extracellular domain", "lacking its associated signal sequence" because a signal sequence is not generally considered part of an extracellular domain. Applicants have amended Claims 4-6 and 14 to delete any reference to an extracellular domain.

The PTO also objects to the use of "hybridize" and "stringent conditions" since what hybridizes depends on the conditions under which the hybridization is carried out, and "stringent conditions" is a relative term. Applicants have amended Claim 14 to specify the conditions under which the hybridization occurs, and have canceled claim 15. Thus, Applicants request that the PTO reconsider and withdraw the indefiniteness rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-20 as lacking a specific, substantial, and credible utility. The PTO asserts that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1446. One of the asserted utilities for the claimed nucleic acids is use as a

diagnostic tool, as well as therapeutically as a target for treatment, based on the data that PRO1446 cDNA is more highly expressed in normal stomach tissue compared to stomach tumor. The PTO has rejected this utility arguing that there is no supporting evidence to indicate that the polypeptide encoded by the claimed nucleic acids of the instant invention is more highly expressed in some normal and tumor tissue compared to their tumor and normal counterparts. The PTO also asserts that the evidence that the polynucleotide is more highly expressed in normal stomach is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to stomach tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. The PTO asserts that without knowing the identity of the tumor, one of skill in the art cannot use the polynucleotides for diagnostic or therapeutic purposes. The PTO also states that the specification does not disclose a correlation between any specific disorder and the altered level of the claimed nucleic acids encoding the polypeptides. The PTO also states that because cancerous tissue is aneuploid, the data is unreliable. Finally the PTO argues that there is no correlation between protein expression and nucleic acid levels.

Applicants respectfully disagree.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention

must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than

not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art**

would be convinced, to a reasonable probability, that the asserted utility is true. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

*The Data in Example 18 are Data Regarding Differential mRNA Levels, **not** Gene Amplification*

Applicants begin by clarifying that the data concerning the differential expression of the PRO1446 gene presented in Example 18 relate to gene expression, **not** gene amplification. The description of Example 18 makes clear that the results were obtained by quantitative PCR amplification of cDNA libraries. It is well known in the art that cDNA libraries are made from mRNA, and reflect the level of mRNA for a particular gene in the source tissue. Thus, Example 18 is reporting a measure of the *expression* of the PRO1446 gene, i.e. mRNA levels, not its *amplification*, i.e. the number of copies of PRO1446 in the genome.

As the PTO has indicated, gene amplification, i.e. an increased number of copies of a gene in the genome, can result from tissue being aneuploid. The PTO states that Sen *et al.* teaches that cancerous tissue is known to be aneuploid, and that higher amplification of a gene does not necessarily mean higher expression in the cancerous tissue. The PTO suggests that the results reported in Example 18 are unreliable because they "are not corrected for aneuploidy." Office Action at 8. The PTO also relies on Pennica *et al.* to teach that "it does not necessarily follow that an increase in gene copy number results in increased gene expression." Office Action at 8 (emphasis added).

Whether or not gene amplification leads to increased gene expression is irrelevant to this particular application. Likewise, whether the differential mRNA expression of the PRO1446 gene reported in Example 18 is due to an increase or decrease in copy number, or alternatively due to an increase or decrease in transcription rates, is simply not relevant. Applicants have

provided reliable evidence that the PRO1446 mRNA is differentially expressed in certain tumors. Whether this differential expression is due to changes in gene copy number, transcription rates, a combination of the two, or some other known or unknown cellular mechanism is simply not relevant to Applicants' asserted utility. It is not clear how Applicants should "correct" the reported results for aneuploidy.

Summary of Applicants' Arguments and the PTO's Position

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed nucleic acids have utility as diagnostic tools for cancer, particularly stomach cancer. Applicants' asserted utility rests on the following argument:

1. Applicants assert they have provided reliable evidence that mRNA for the PRO1446 polypeptide is expressed at least two-fold higher in normal stomach compared to stomach tumor, and therefore the claimed nucleic acids are useful as diagnostic tools. Applicants are not asserting that the claimed nucleic acids will necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers.

2. Applicants submit that it is not necessary to know what role the PRO1446 gene plays in cancer to use its differential expression as a diagnostic tool.

3. It is not required to prove that the PRO1446 polypeptide is also differentially expressed in certain tumors to establish the utility of the claimed nucleic acids.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it provides no information regarding the biological significance of the differential expression, or whether it is the cause or result of the tumors;

2. The PTO cites Sen *et al.* and Pennica *et al.* to support its position that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression;

3. The PTO concludes that based on the cited literature, the data of Example 18 do not necessarily indicate anything significant regarding the claimed nucleic acids. Therefore, further

research needs to be done to use PRO1446 as a cancer diagnostic tool. *See* Office Action at 7-10.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, (attached as Exhibit 2) which establishes the reliability of the data of Example 18. Knowing the biological significance of the data, or the role of PRO1446 in cancer, is not necessary to use the claimed nucleic acids as cancer diagnostic tools. Second, as discussed above and can be seen from Applicants' summary of their argument, Applicants submit that any lack of correlation between gene amplification and gene expression is not at issue in this application and therefore the Sen *et al.* and Pennica *et al.* references are not relevant. Third, Applicants submit that given the well-established correlation between a change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1446 protein is likely differentially expressed in certain tumors. However, utility for the pending claims does not rely on whether the encoded polypeptide is overexpressed, and as such whether or not increased levels of PRO1446 mRNA correlate with increased levels of PRO1446 protein is <u>not</u> presently an issue.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

<u>Applicants have established that the Gene Encoding the PRO1446 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue and is Useful as a Diagnostic Tool</u>

Applicants first address the PTO's argument that the evidence of higher expression of the gene encoding the PRO1446 polypeptide in normal stomach tissue compared to stomach tumor is insufficient because it does not disclose what the normal level of expression is, does not indicate how high the expression level is compared to stomach tumor, it lacks statistical correlation, and because the type or kind of tumor, even if it is malignant, is not described. Applicants also

address the PTO's argument that because cancerous tissue is aneuploid, the data is unreliable. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed nucleic acids related to the gene encoding the PRO1446 polypeptide.

Applicants have submitted herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (Exhibit 2). In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that a lack of known role for PRO1446 in cancer does not prevent its use as a diagnostic tool for cancer. Whether the differential expression of PRO1446 is a cause or result of the stomach tumors is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1446 is differentially

expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue.

The PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utilty because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a particular condition are patentable (*see, e.g.,* U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No. 6,162,604 submitted herewith as Exhibits 3-5), even though they may or may not cause the disease itself. Similarly, the present nucleic acids which are useful for determining whether an individual has cancer are useful regardless of whether or not they are the cause of the cancer.

The PTO also argues that because cancerous tissue can be aneuploid, and the data in the instant application was not corrected for aneuploidy, "[a] higher amplification of a gene does not necessarily mean higher expression or lower in a tissue, but can merely be an indication that the cancer tissue is aneuploid." Office Action at 8. The PTO relies on a single reference, Sen, 2000, Curr. Opin. Oncol. 12:82-88 (hereinafter Sen).

Applicants agree that Sen teaches that most cancerous tissues are aneuploid, and that it is possible that the results reported in Example 18 may be due to aneuploidy in the tumor cells tested. However, as discussed above, Applicants fail to see how whether the differential expression reported in Example 18 is due to aneuploidy or not is relevant to the utility of the disclosed nucleic acids. Regardless of whether the differential expression of the gene encoding PRO1446 is a result of increased or decreased transcription of the gene, aneuploidy, or some other regulatory mechanism, the fact remains that it is more highly expressed in normal stomach compared to stomach tumor, and it is therefore useful as a diagnostic tool for cancer since it can be used as a molecular marker for cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1446 cDNA between normal stomach and stomach tumor. Therefore, it follows that expression levels of the PRO1446 gene can be used to distinguish stomach tumor tissue from normal stomach. The PTO has not offered any significant arguments or evidence to the contrary. Applicants have therefore established a utility for the claimed nucleic acids as diagnostic tools for cancer, particularly stomach tumors.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

While not necessary to establish the utility of the claimed nucleic acids, Applicants have asserted that there is a direct correlation between changes in the level of mRNA and changes in the level of expression of the corresponding protein.

The PTO, relying on a single example of one gene reported in Pennica, states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on the statement from Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient. Office Action at 8-9. As an aside, it should be noted that this result may not even be real, as the authors explain: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the apparent amplification observed for *WISP-2* may be caused by another gene in this amplicon." Pennica at 14722 (emphasis added).

The reference relied on by the PTO is irrelevant for two reasons. First, as Applicants have stated above, whether an increase in gene copy number leads to an increase in gene expression or protein expression is not presently an issue in this application. The data of Example 18 reflects mRNA data as assessed by examining cDNA created from mRNA. It is not gene amplification data. Thus, even if the lack of correlation between DNA copy number and mRNA level in Pennica is real, Pennica says nothing about a lack of correlation between the level of mRNA and the level of protein expression – Pennica did not even look at protein expression.

Second, because the claims have been amended such that the claimed nucleic acids are not defined by the sequence of the polypeptide they encode, the question of whether there is a correlation between changes in mRNA level and changes in the level of the corresponding protein **is not presently at issue**. However, Applicants submit that they have established for the record that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein. Given Applicants' evidence of differential expression of the mRNA for the PRO1446 polypeptide in stomach tumors, it is more likely than not that the PRO1446 polypeptide is also differentially expressed.

Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 6). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 7), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 8) and (4th ed. 2002) (submitted herewith as Exhibit 9)). Figure 9-2 of Exhibit 8 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 8 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 8 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 8 at 453 (emphasis added). Thus, as established in Exhibit 8, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 9, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 9 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 9 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 9 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 9 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 10) which states "having

acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 11. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 11 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 11 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 11 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 12, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

As discussed above, whether or not increased levels of PRO1446 mRNA correlate with increased levels of PRO1446 protein is not presently an issue. However, Applicants submit that together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants

submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1446 mRNA is expressed at a higher level in normal stomach compared to stomach tumor, the PRO1446 polypeptide will also be expressed at a higher level in normal stomach compared to stomach tumor.

The Claimed Nucleic Acids would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between changes in gene expression and changes in protein expression for PRO1446, which Applicants submit is not true, nucleic acids related to a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 6, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 13), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 14). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between changes in gene expression and changes in protein expression. However, even when this is not the case, a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed nucleic acids.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that a gene differentially expressed in certain tumors can be used as a diagnostic tool. As stated above, the article by Sen provides no support for the PTO's position since whether cancer is aneuploid or not is irrelevant to the utility of the

claimed nucleic acids. Likewise, whether or not gene amplification leads to increased gene expression is not relevant, and thus the article by Pennica *et al.*, 1998, PNAS USA 95:14717-14722, does not support the PTO's position.

Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed nucleic acids can be used as diagnostic tools for cancer, particularly stomach cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Nucleic Acids

Applicants next address the PTO's assertions that there is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1446. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1446 gene in certain types of cancer cells, along with the declarations discussed above, provide a specific utility for the claimed nucleic acids.

As discussed above, there are significant data which show that the mRNA encoding the PRO1446 polypeptide is expressed at least two-fold higher in normal stomach tissue compared to stomach tumor. These data are strong evidence that the gene encoding the PRO1446 polypeptide is associated with stomach tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the gene encoding PRO1446 with a specific disease. This is a specific utility – it is not a general utility that would apply to the broad class of nucleic acids.

Conclusion

The PTO has asserted two arguments for why there is a lack of a substantial utility: (1) that the data reporting differential expression of the PRO1446 gene in certain cancers is not

reliable and does not establish a correlation between the differential expression and the tumors; and, (2) that because there is no necessary correlation between gene amplification and protein expression, the claimed nucleic acids cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the data in Example 18 are real and significant. This declaration also indicates that given the at least two-fold difference in expression levels, the disclosed nucleic acids and corresponding polypeptides have utility as cancer diagnostic tools. Applicants have demonstrated that it is not necessary to know the cause or consequence of the differential expression of PRO1446 nucleic acids and polypeptides in stomach tumors in order to use them as diagnostic tools for cancer.

Next, Applicants assert that whether the encoded polypeptide is also differentially expressed in certain tumors is currently not at issue in this application. However, Applicants submit that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reasoning or evidence to the contrary.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed nucleic acids because the PRO1446 gene and polypeptide are differentially expressed in stomach tumors compared to normal stomach tissue. This is not a general utility that would apply to the broad class of nucleic acids.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed nucleic acids as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to

> demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed nucleic acids as diagnostic tools as set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The PTO rejected Claims 1-20 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

The PTO also states that even if a specific and substantial utility were established, they are enabled only for polynucleotides of SEQ ID NO: 113 and fragments that are usable as hybridization probes, they are not enabled for claims to polynucleotides with 80-99% sequence identity to SEQ ID NO: 113, or those which encode polypeptides with 80-99% sequence identity to SEQ ID NO: 114, or those which hybridize to any of the above because there is no structural or functional information provided in the specification. The PTO states that there is insufficient guidance regarding how to make PRO1446 polynucleotide variants. The PTO also states that the hybridization claims are not enabled because they do not recite that the polynucleotide encodes a protein having a specifically disclosed activity. The PTO next asserts that even if utility of the claimed nucleic acids as hybridization probes is established, degenerate sequences are not enabled.

As an initial matter, Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed nucleic acids.

As amended, the pending claims are to nucleic acids that have at least 95% or 99% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO:113 or its the full-length coding sequence, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203285, and wherein the nucleic acid is "more highly expressed in normal stomach compared to stomach tumor" or "hybridizes to the complement of a nucleic acid of SEQ ID NO: 113" under the specified stringent conditions. Other claimed nucleic acids are those which hybridize to the recited sequences under stringent conditions.

Applicants submit that the claimed nucleic acids are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences related to SEQ ID NO: 113. Likewise, Applicants have disclosed how to determine if the claimed nucleic acids are differentially expressed in stomach tumors compared to normal stomach tissue (*see, e.g.,* Example 18 beginning at paragraph [0529] of the specification). Finally, it is well-known in the art how to determine if a nucleic acid hybridizes to the disclosed sequences under the specified stringent conditions. Thus, one of skill in the art would know how to make the claimed nucleic acids.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO1446 gene is differentially expressed in stomach tumors. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed nucleic acids as diagnostic tools. For example, nucleic acids which have at least 95% or 99% sequence identity to the disclosed sequences and are "more highly expressed in normal stomach compared to stomach tumor" can be used as diagnostic tools since the claimed nucleic acids are themselves differentially expressed in certain tumors. A claimed nucleic acid which has at least 95% or 99% sequence identity to the disclosed sequences and "hybridizes to the complement of a nucleic acid of SEQ ID NO: 113," or which hybridizes to the disclosed sequences under the specified stringent conditions can be used as a hybridization probe to detect the expression of the PRO1446 gene, making it useful as a diagnostic tool. Given the skill in the art and the disclosure of how to make and use the claimed nucleic acids, Applicants request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO has rejected Claims 1-5 and 15-20 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. According to the PTO, because the claims do not require that the claimed nucleic acids encode a particular protein, or that any encoded protein possess any particular biological activity, the claims fail the written description requirement.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112 , first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); see also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. See e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO: 113, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 113, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203285, with the functional recitation as amended: "more highly expressed in normal stomach compared to stomach tumor" or "wherein said isolated nucleic acid hybridizes to the complement of a nucleic acid of SEQ ID NO: 113" under the specified conditions. Other claimed nucleic acids are those which hybridize to the nucleic acid sequence of SEQ ID NO: 113, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO: 113, the full-length coding sequence of the cDNA deposited under ATCC accession number 203285, or the complements thereof, under the specified stringent conditions. We turn first to the claims which recite specific high stringency hybridization conditions.

In *Enzo Biochem v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002), the Court held that functional descriptions of genetic material may satisfy the written description requirement. In so holding, the Court gave judicial notice to the USPTO's Manual of Patent Examining Procedure, which provides that the written description requirement may be satisfied when the disclosure provides sufficiently detailed identifying characteristics, such as "complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics." *Id.* at 964, quoting 66 Fed. Reg. at 1106 (emphasis in original). In *Enzo*, the Court found describing nucleic acids based on their ability to hybridize to another nucleic acid sequence which was adequately described may be an adequate description of the nucleic acid. This is because the hybridization function of a nucleic acid is dependent on the sequences of the nucleic acid – a disclosed function which is coupled with a known correlation between function and structure. The Court favorably discussed the PTO's example wherein "genus claims to nucleic acids based on their hybridization properties...may be adequately described if they hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Id.* at 967 (citing *Application of [Written Description] Guidelines*, Example 9) (emphasis added).

Applicants submit that the stringent hybridization conditions specified in the pending claims, alone or in combination with the recited percent sequence identity, result in all species

within the genus being structurally similar. As the *Enzo* Court noted, Examples 9 and 10 of the Application of Written Description Guidelines (hereinafter "Guidelines") make clear that specifying hybridization under highly stringent conditions yields "structurally similar DNAs." Guidelines, Example 9 at page 36. The analysis of a genus claim in Example 10 of the Guidelines states:

> [T]urning to the genus analysis, the art indicates that *there is no substantial variation within the [claimed] genus because of the stringency of hybridization conditions which yields structurally similar molecules*. The single disclosed species is representative of the genus because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Guidelines, Example 10 at page 39 (emphasis added).

Given the level of skill in the art, specifying highly stringent conditions leads to "no substantial variation within the [claimed] genus," and therefore a skilled artisan would recognize that the Applicants were in possession of the necessary common attributes or features of the genus. This is contrary to the PTO's argument that the claimed sequences do not possess "any particular conserved structure, or other disclosed distinguishing feature." Office Action at 15. The common element or attribute of the claimed genus is that species of the genus are structurally related to SEQ ID NO: 113, such that they hybridize to SEQ ID NO: 113 or the related sequences under the specified high stringency conditions recited in the claims.

The present situation is not analogous to *Fiddes v. Baird*, 30 U.S.P.Q. 2d 1481, cited by the PTO. Unlike *Fiddes*, where arguably the structure of other mammalian sequences could not be conceived based on a single species of the genus, here the skill in the art is such that the sequence of nucleic acids which hybridize to SEQ ID NO: 113 under the conditions specified can be conceived. Here, the claimed genus is defined by its structure – members of the genus hybridize under the specified conditions to the specified sequences, each of which are adequately described in the specification.

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO: 113 with the functional recitation "more highly expressed in normal stomach compared to stomach tumor" are also adequately described. In Example 14 of the written description training materials, the written description

requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in stomach tumors. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which are attached hereto as Exhibits 15-20.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 113, by specifying the high stringency conditions under which hybridization occurs, and by describing the gene expression assay, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO rejects Claims 1-10 and 12-20 as anticipated under 35 U.S.C. § 102(b) by Lal *et al.* (WO200000610 A2, January 2000) (hereinafter Lal), which was published on January 6, 2000, and by Jacobs *et al.* (WO200009552 A1, February 2000) (hereinafter Jacobs), which was published on February 24, 2000. The PTO states that Lal discloses nucleotides encoding the amino acid sequence of SEQ ID NO: 114 of the instant invention, hybridization probes, vectors, and host cells. The PTO states that Jacobs discloses nucleotides encoding the amino acid sequence of SEQ ID NO: 114 of the instant invention, hybridization probes, vectors, and host cells.

As discussed above, Applicants claim priority to PCT Application PCT/US00/23328 filed 8/24/2000, and to US Provisional Application 60/101475 filed 9/23/1998. The sequences of SEQ ID NOs: 113 and 114 were first disclosed in US Provisional Application 60/101475 filed 9/23/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. For the reasons detailed above, Applicants have established that the claimed nucleic acids have utility and are enabled. The instant application is therefore entitled to a priority date of at least August 24, 2000.

The publication date of Lal is January 6, 2000, and the publication date of Jacobs is February 24, 2000. The publication dates of both cited references are less than a year before either the September 23, 1998 or August 24, 2000 priority dates claimed for the instant application. Therefore, neither Lal nor Jacobs are available as prior art under 35 U.S.C. § 102(b). Applicants therefore respectfully request that the rejection under 35 USC §102(b) be withdrawn.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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